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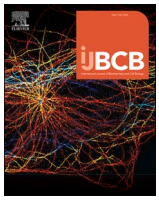

Ataxia-telangiectasia mutated and ataxia telangiectasia and Rad3-related kinases as therapeutic targets and stratification indicators for prostate cancer

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ABSTRACT

The DNA damage response is an integral part of a cells' ability to maintain genomic integrity by responding to and ameliorating DNA damage, or initiating cell death for irrepairably damaged cells. This response is often hijacked by cancer cells to evade cell death allowing mutant cells to persist, as well as in the development of treatment resistance to DNA damaging agents such as chemotherapy and radiation. Prostate cancer (PCa) cells often exhibit alterations in DNA damage response genes including ataxia telangiectasia mutated (ATM), correlating with aggressive disease phenotype. The recent success of Poly (ADP-ribose) polymerase (PARP) inhibition has led to several clinically approved PARP inhibitors for the treatment of men with metastatic PCa, however a key limitation is the development of drug resistance and relapse. An alternative approach is selectively targeting ATM and ataxia telangiectasia and Rad3-related (ATR) which, due to their position at the forefront of the DDR, represent attractive pharmacological targets. ATR inhibition has been shown to act synergistically with PARP inhibition and other cancer treatments to enhance anti-tumour activity. ATM-deficiency is a common characteristic of PCa and a synthetic lethal relationship exists between ATM and ATR, with ATR inhibition inducing selective cell death in ATM-deficient PCa cells. The current research highlights the feasibility of therapeutically targeting ATR in ATM-deficient prostate tumours and in combination with other treatments to enhance overall efficacy and reduce therapeutic resistance. ATM also represents an important molecular biomarker to stratify patients into targeted treatment groups and aid prognosis for personalised medicine.

1. Prostate cancer

The prostate is a male accessory gland, which is highly susceptible to chronic inflammation in later life, an event that increases the probability of malignant transformation and progression (Stark et al., 2015; Cai et al., 2019). Given this, it is unsurprising that prostate cancer (PCa) is the most commonly diagnosed cancer among men in the UK, accounting for approximately 11,900 deaths each year (Cancer Research UK, 2018). The dependence on androgens for prostate development and function positions the androgen receptor (AR) as a crucial component in prostate homoeostasis (Banerjee et al., 2018). Aberrant signalling via the AR, a transcription factor that upon binding androgen dihydrotestosterone translocates to the nucleus to regulate numerous genes involved in proliferation and differentiation, promotes prostate carcinogenesis (Culig and Santer, 2014). Whilst alterations in AR-related signal transduction pathways are predominantly associated with PCa development and progression, many patients with advanced disease also possess genomic alterations in DNA damage response (DDR) genes (Abida et al., 2019; Castro et al., 2019). For example, analysis of 150 metastatic PCa primary samples identified BRCA2 and ATM as the most frequently mutated DDR genes, occurring respectively in 13% and 7.3% of biopsies (Robinson et al., 2015). Consequently, this impairs PCa cells' ability to ameliorate DNA damage tipping the balance to genomic instability, an enabling characteristic of cancer (Hanahan and Weinberg, 2011; Lozano

Abbreviations: AR, androgen receptor; PCa, prostate cancer; DDR, DNA damage response; ATM, (ataxia telangiectasia mutated); ATR, (ATM and Rad3-related); IR, ionising radiation; DSBs, double-stranded breaks; MRN, Mre11-Rad50-Nbs1; HR, homologous recombination; ssDNA, single-stranded DNA; SSBs, single-stranded breaks; RPA, replication protein A; A-T, ataxia telangiectasia; MCL, mantle cell lymphoma; CRC, colorectal cancer; ICI, immune checkpoint inhibition; PARPi, PARP inhibitors; mCRPC, metastatic castration-resistance prostate cancer; IHC, immunohistochemistry; NGS, next generation sequencing; ATRi, ATR inhibition.

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et al., 2021). Mutations in DDR-related genes have been correlated with higher disease recurrence, aggressiveness of disease and poor prognosis in prostate cancer patients (Nientiedt et al., 2021).

2. DNA damage repair

In order to maintain genomic integrity, cells have evolved a highly conserved DNA damage response (DDR) underpinned by integrated kinase-driven networks co-ordinating DNA damage repair mechanisms (Carrassa and Damia, 2017). Strict coordination between cell cycle control and DNA repair pathways allow cells to identify DNA damage and subsequently arrest cell cycle progression until damage is ameliorated or, if irreparable, to initiate programmed cell death (Maréchal and Zou, 2013). Aberrations in DDR signalling and cell cycle checkpoints can allow cells harbouring DNA mutations to persist, consequently contributing to the development of cancer (Kastan and Bartek, 2004).

2.1. DNA damage response signalling via ATM and ATR kinases

ATM (ataxia telangiectasia mutated) and ATR (ataxia telangiectasia and Rad3-related) are serine/threonine kinases integral in regulating the DDR. ATR and ATM respond to DNA damage via phosphorylation of the checkpoint kinases CHK1 and CHK2, respectively (Smith et al., 2010), allowing activation of specific cell cycle checkpoints to delay cell cycle progression and promotion of DNA repair pathways (Matsuoka et al., 2007). However, whilst it was originally considered that the ATM/Chk2 and ATR/Chk1 pathways have separate and specific responses, it is now evident that these pathways are inter-linked with crosstalk between the two kinases in response to genotoxic stress (Schlam-Babayov et al., 2021).

While their roles can overlap, ATM primarily senses and responds to DNA double-stranded breaks (DSBs) whereby ATM/Chk2 modulates cell cycle control via phosphorylation of MDM2, subsequently stabilising p53 and preventing its degradation (Cheng et al., 2009). ATM and Chk2 can also directly activate p53 via phosphorylation, inducing G1 cell cycle arrest and preventing cells with damaged DNA from G1/S

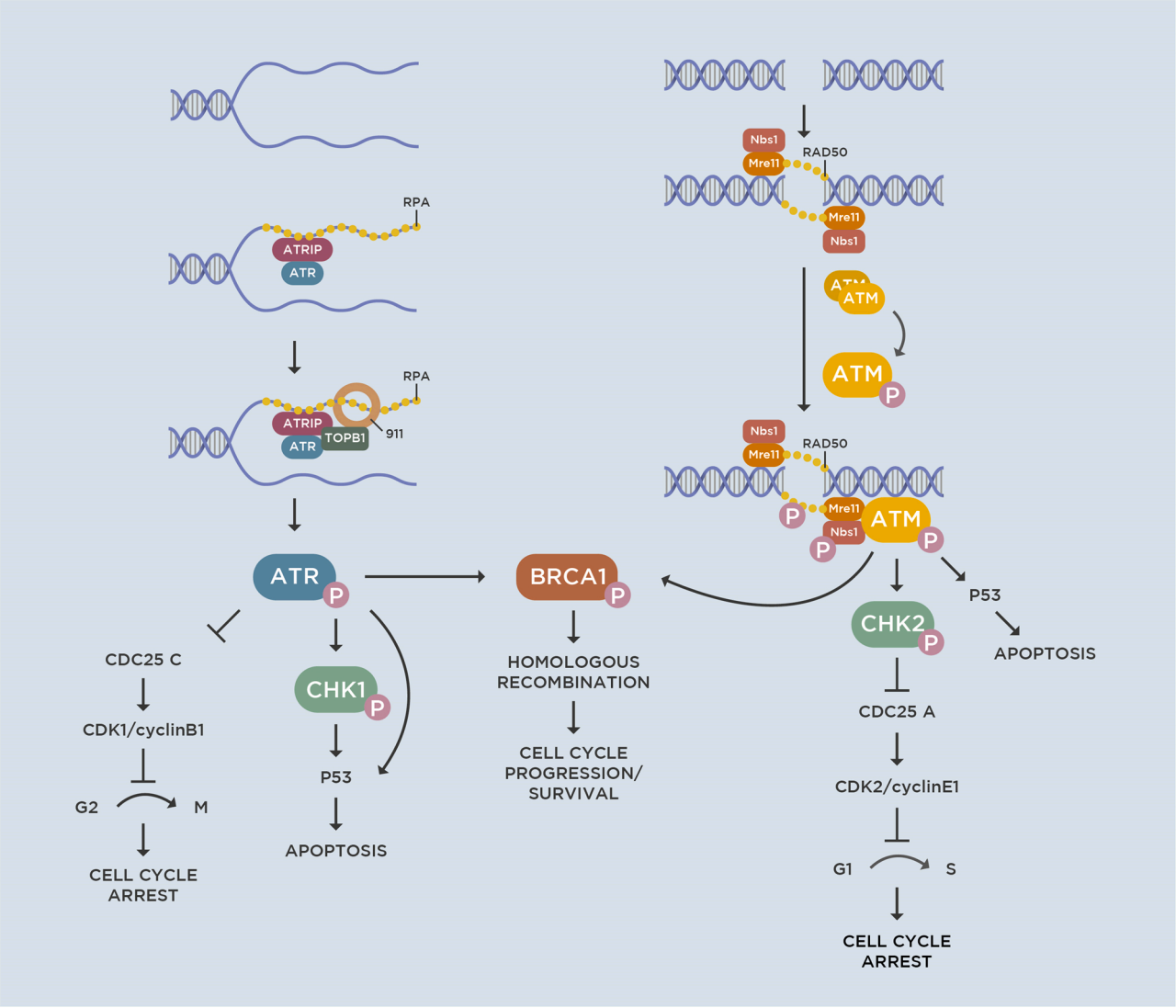

Fig. 1. ATM and ATR signalling cascade in the DNA damage response in prostate cancer. ATR is recruited to sites of stalled replication forks via ATRIP, subsequently recruiting TOPB1 and 9-1-1 to the site. This induces ATR phosphorylation and induction of Chk1 signalling cascade to inhibit cell cycle arrest at G2-M, trigger apoptosis via p53, or phosphorylate BRCA1 for HR-mediated repair. ATM is recruited to sites of double stranded DNA damage via the MRN complex, initiating ATM phosphorylation and subsequent activation of Chk2 signalling cascade, to inhibit cell cycle arrest at G1-S, trigger apoptosis via p53, or phosphorylate BRCA1 for HR-mediated repair.

transition (Stracker et al., 2013). ATM also facilitates DNA repair where, upon its recruitment to DSB sites via the Mre11-Rad50-Nbs1 (MRN) complex, it plays a crucial role in homologous recombination (HR) (Lee and Paull, 2005; Bakr et al., 2015). In this case ATM facilitates DSB end resection to generate single-stranded DNA (ssDNA) regions required for HR initiation (Bakr et al., 2015).

ATR on the other hand can sense a wide range of DNA lesions such as single-stranded breaks (SSBs), as well as ssDNA present at stalled replication forks or at resected DSBs (Matsuoka et al., 2007; Maréchal and Zou, 2013). Stalled replication machinery can induce cytotoxic DSBs, therefore their resolution is crucial for maintaining genomic integrity. Replication protein A (RPA)-coated ssDNA stimulates ATRIP-mediated ATR recruitment to sites of SSBs and DSBs, as well as stalled replication forks, ultimately facilitating fork resolution and DNA repair pathways (Saldivar et al., 2017). A key feature of ATR's response to replication stress and DNA damage is promoting transient cell cycle arrest. Here, ATR/CHK1 action promotes the S-phase via CHK1-mediated degradation of the CDC25A/B/C phosphatases that inhibit CDK1 and CDK2. This in turn prevents entry into mitosis (G2/M arrest) until DNA damage/replication stress is resolved (Saldivar et al., 2017; Simoneau and Zou, 2021). Interestingly, ATM/Chk2 is also able to degrade CDC25A during G2/M transition to prevent cell cycle progression in response to IR (Weber and Ryan, 2015). Overall, ATR promotes replication fork stabilisation and resolution, DNA repair and cell cycle arrest.

The observation that ATM and ATR have overlapping involvement in facilitating cell cycle checkpoint progression and involvement in DNA repair pathways highlights the importance of the coordination and crosstalk between these kinases in coordinating an efficient DDR (Maréchal and Zou, 2013; Yan et al., 2014). Persistent DNA damage poses a significant threat to genomic stability, with the inability to repair conferring an increased risk of developing diseases such as cancer (Chakraborty and Hiom, 2021). Given their fundamental roles in coordinating multiple components of downstream signal transduction pathways, ATM and ATR activity must be strictly coordinated in order to prevent irregular cell cycle control, DNA repair or cell death mechanisms (Matsuoka et al., 2007). The in-depth roles of ATM and ATR signalling pathways in the DDR have previously been extensively reviewed (Smith et al., 2010; Blackford and Jackson, 2017), and this review will focus primarily on their potential as inhibitory targets and biomarkers for the treatment of prostate cancer.

2.2. DNA damage repair in prostate cancer

Cancer cells are able to hijack a variety of cellular signalling systems to enhance proliferation potential and survival, for example, promotion of defective DDR pathways to drive genomic instability and mutational burden (Li et al., 2021). Often, defects in these pathways arise due to germline or somatic mutations in DDR genes. The tumour suppressor gene TP53, termed the guardian of the genome, is among the most frequently mutated genes in many human cancers (Blandino and Di Agostino, 2018), driving dysregulated cell cycle control and increased susceptibility to numerous cancers.

ATM mutations also frequently occur in a multitude of different cancers, often resulting in functional deletion of the ATM protein which can impact the activity of its downstream targets, such as TP53, CHK2 and BRCA1. In fact, deletion of ATM causes the disease ataxia telangiectasia (A-T) and is associated with increased lifetime risk of developing cancer by 20–30% (Choi et al., 2016). Mutations in DDR genes are a common feature of metastatic castration-resistance prostate cancer (mCRPC) patients, accounting for approx. 35–40% cases, generally increasing during PCa progression (Wengner et al., 2020). These DDR-deficient tumours often exhibit unique genomic characteristics and can coincide with aggressive phenotypes (Rafiei et al., 2020). Whilst alterations in many DDR genes have been observed, ATM and BRCA2 are among the most commonly mutated genes found in mCRPC (Wengner et al., 2020). Ultimately, dysregulation of these proteins and their transduction pathways cause insufficient cellular repair and oncogenic stress, contributing to the development of cancer (Staniszewska et al., 2021).

On the other hand, ATR function is almost never completely lost. Whilst mutations or reduced expression are occasionally observed, for example in Seckel syndrome, relative to ATM mutations these are rare (Karnitz and Zou, 2015). Studies investigating ATR silencing showed that ATR depletion resulted in embryonic lethality in mice, once again highlighting importance of this gene for health (Brown and Baltimore, 2000). With regards to cancer, ATR appears to be extremely important for the survival of malignant cells. Dysregulation of other DDR genes or oncogenic signalling can induce replicative stress by promoting cell cycle progression, which in turn stimulates the ATR/Chk1 pathway (Karnitz and Zou, 2015). Overall, this highlight cancer cells' dependency on ATR for survival when other oncogenic pathways are impaired. Given the importance of DDR proteins in cell cycle control and DNA damage repair, functional inadequacy of these proteins can allow cells to bypass repair pathways and cell cycle checkpoints, promoting unhindered growth of malignant cells.

3. DNA damage repair inhibition

The DDR can be regarded as the Achilles' heel of cancer as while deficiencies in DNA repair contribute to many carcinogenic hallmarks [replicative immortality, resistance to cell death and genomic instability (Hanahan and Weinberg, 2011)], it also represents a vulnerable target for inhibition due to cancer cells' substantial reliance on these pathways (Carrassa and Damia, 2017) Fig. 1.

Many cancer treatments such as chemotherapy and radiotherapy rely on the generation of severe DNA damage in rapidly dividing cells (e.g. cancer cells) to induce cell death, however cancer cells can harness specific DDR pathways to ameliorate this damage, rendering tumours insensitive to treatment (Weber and Ryan, 2015). Upon generation of DSBs, cells rely on an intact HR pathway to repair DNA damage efficiently with minimal chance of error. Mutations in key HR-related genes such as ATM and BRCA1/2 position these as attractive targets in cancer therapy, with HR-deficient tumours exhibiting enhanced sensitivity to DDR inhibition (Staniszewska et al., 2021). Considering this, targeting key mediators/effectors of the DDR has become an attractive approach to overcome current treatment limitations, by inhibiting cells' ability to repair DNA and subsequently enhance susceptibility to genotoxic agents (Wengner et al., 2020; Li et al., 2021). Additionally, tumours exhibiting deficiencies in DDR components represent vulnerable targets to exploit via synthetic lethality (Weber and Ryan, 2015). Overall, this presents an interesting therapeutic approach for DDR genes i.e. utilising the cause of cancer to subsequently treat the disease and is validated by the induction of synthetic lethality in BRCA-mutant cancers via PARP inhibitors (Staniszewska et al., 2021). Overall, targeting the DDR represents a promising and selective strategy in the fight against cancer.

3.1. ATM/ATR as drug targets

ATM and ATR represent attractive pharmacological targets due to their position at the forefront of the DDR cascade. Activation of these kinases are the first steps characterised in downstream signal transduction pathways, phosphorylating hundreds of proteins to facilitate DNA repair and cell cycle control (Schlam-Babayov et al., 2021).

Hence, it is unsurprising given ATM's crucial role in activating DDR pathways in response to IR and other DNA damaging agents that studies in ATM-knockout mice showed hypersensitivity to IR treatment (Barlow et al., 1996). Similarly, pancreatic cancer cells in which ATM was silenced showed significantly increased sensitivity to radiation, however response to chemotherapy was not affected (Ayars et al., 2017). The common loss of p53 function exhibited by many tumours contributes to radio-/chemo-therapy resistance due to impaired p53-mediated

apoptosis (Nghiem et al., 2001). Synergism between combined p53 and ATM knockdown has been shown to further sensitise cancer cells to chemotherapeutic agents, whereas in p53-WT cells with ATM inhibition this tumour suppressor actually protects the cells from genotoxic damage and cell death, highlighting the importance of p53 in this context (Jiang et al., 2009).

Conversely, another potential approach to modulate ATM activity for the purpose of sensitising cancer cells to chemotherapy is via kinase activation rather than inhibition. A feature of cancer cells with chemoresistance is compaction of chromatin. ATM functions in decondensation of chromatin suggesting that activation of ATM through histone deacetylase inhibition could remodel the chromatin to overcome this and thus re-sensitise cancer cells to these drugs. However, it is important to consider that ATM also functions in chromatin relaxation to allow DDR machinery access to the damaged DNA, therefore this technique could be a double-edged sword (Cremona and Behrens, 2014). Conceptually, ATR inhibition could also show potential for the re-modelling of chromatin with genotoxic outcomes. ATR performs a critical role in DNA-damaged cells to prevent premature chromatin condensation, therefore inhibition of ATR could sensitise cells to such DNA damage inducing treatments, causing premature cell death through premature chromatin condensation (Nghiem et al., 2001).

As previously noted, unlike ATM, mutations in ATR are rare positioning it as an attractive anti-neoplastic target due to its' consistent activity and key roles in mediating cell cycle progression (Gorecki et al., 2020). ATM mutations frequently observed in cancers cause ATM deficiency which therefore forces cells that are reliant on ATR-mediated DNA damage repair to compensate in some way in order to maintain genomic integrity. Selective inhibition of ATR therefore represents a promising approach to induce cell death in these types of cancers (Kwok et al., 2016). In mantle cell lymphoma (MCL) for example, ATM loss-of-function cells exhibited enhanced sensitivity to ATR inhibition in comparison to wild-type (WT) MCL cells (Menezes et al., 2015). A study by Dunlop et al. (2020) revealed that ATM loss can be used as a predictive biomarker in assessing cancer response to combined ATR inhibition with chemotherapy. Experimentation in PDAC cells showed that a complete loss of ATM function is required to sensitise cells to ATR inhibition (via AZD6738 & Gemcitabine), whereas cells with ATM reduced expression rather than knockout didn't display hypersensitivity. Overall, it is clear that ATR inhibition via small molecule inhibitors represent an effective treatment choice in cancers with ATM-deficiency, however ATM expression should be measured in patients to determine sensitivity to such treatments.

In an ATM-deficient setting, sensitivity to PARP inhibition is also observed. For example, colorectal cancer (CRC) cell lines following shRNA-mediated downregulation of ATM exhibit increased sensitivity to Olaparib (PARP inhibitor). This was evident not just through shRNA but also via combined treatment with Olaparib and KU55933 (ATM inhibitor). Interestingly, sensitivity with this combined treatment was further enhanced upon p53 silencing (Wang et al., 2017). Discussion on ATM-deficient PARP inhibitor sensitivity will be further discussed later in the context of prostate cancer.

Aside from radiation, chemotherapy and selective DDR pathway inhibition, targeting ATM and ATR has also been explored as a factor for the enhancement of anti-tumour immunotherapy. Whilst the discovery of immune checkpoint inhibition (ICI) via the targeting of CTLA-4 and PD-1/PD-L1 has been nothing short of a revolution, a major limitation of this approach is that only a relatively small pool of cancers are immunogenic enough to respond effectively to this treatment (Goff et al., 2021). ATM deficiency is linked with enhanced cancer immunogenicity through upregulation of type 1 interferon (IFN) signalling (Härtlova et al., 2015). Research by Zhang et al. (2019) found that ATM silencing in vivo not only enhanced interferon signalling but also upregulated the expression of PD-L1 in a pancreatic cancer mouse model, enhancing the sensitivity to PD-L1 blockade with radiotherapy. Whilst the upregulation of PD-L1 and increased immunogenicity provides enhanced sensitivity to PD-L1 blockade, another approach is to downregulate PD-L1 to mediate cytotoxic T-cell-mediated cell death. Cancer cells can evade immune recognition by binding of PD-L1 to PD-1 on tumour-infiltrating T-cells, deactivating them and hindering an anti-tumour immune response. ATR inhibition decreased PD-L1 expression in various cancer cell lines, subsequently re-sensitising cells to CD8 + T cell-mediated killing, suggesting this approach could be combined with other immunotherapies such as CTLA-4 blockade (Sun et al., 2018). Overall, these studies suggest ATM and ATM can be exploited to provide rational combined therapy with ICI and radiation which may lead to enhanced therapeutic efficacy.

3.2. ATM/ATR inhibition in prostate cancer

3.2.1. Targeting the DNA damage response in PCa

Given that prostate cancer is a substantially heterogenous disease, it is surprising that advanced PCa treatments are not currently stratified against molecular characteristics.

Hormonal therapy, surgery, radiation and chemotherapy have been standard care options for men with the disease, however new therapeutic interventions are required to overcome the limitations of these techniques (Mateo et al., 2020).

In PCa, androgens promote resistance to radiation and chemotherapy through upregulation of DDR genes. Interestingly, targeting the DDR pathway has become a novel approach in the treatment of metastatic prostate cancer with the use of PARP inhibitors (PARPi). Olaparib and Rucaparib were the first PARPis to be FDA-approved in 2020 for the treatment of men with mCRPC who were no longer responding to hormonal therapy and were expressing mutant HR repair genes (U.S. Food and Drug Administration, 2020b, 2020a). Patients with mCRPC presenting HR defects respond well to PARP inhibition and this improves survival, justifying the use of molecular stratification for differentiating subsets of patients for precision medicine approaches to treatment (Neeb et al., 2021). However, whilst PARPi's have benefits outlined above, a key limitation is the development of drug resistance and relapse (Wengner et al., 2020).

3.2.2. ATM mutations in PCa as potential biomarkers

The importance of ATM in the DDR has been substantially discussed in this review, and germline heterozygous ATM deletions are found in approximately 1% of the population who have a predisposition to a variety of cancers (Choi et al., 2016). A study comparing next generation sequencing (NGS) data from 5560 PCa cases compared to 3353 controls revealed that inheritance of pathogenic germline ATM variants increase the risk of developing PCa by four-fold, as well as promoting earlier onset of the disease (Karlsson et al., 2021). Whilst this study didn't establish a correlation between ATM mutation and aggressive phenotype, another multi-centre study identified that the prevalence of ATM alterations appears to correlate with PCa aggression, with tumours derived from 692 metastatic PCa patients exhibiting significantly higher mutant ATM expression compared with localised PCa patients from the Exome Aggregation Consortium (53,105 persons) (Pritchard et al., 2016). Na et al. (2017) also analysed germline ATM mutations alongside BRCA1/2 mutations in PCa patients, finding a positive correlation between mutational burden and lethal disease in comparison to indolent (low risk) tumours. This coincided with shorter survival time and younger age at death, highlighting the potential use of assessing germline mutations in these three DDR genes to stratify patients between indolent and lethal disease. Additionally, germline mutational rates for ATM, alongside BRCA2 and MSH2, can stratify between high vs low grade PCa. In particular, ATM mutation carrier rate was revealed to be 2.12% in high-grade compared to 0.20% in low-grade tumours. Furthermore, in comparisons of Gleason scores, mutant ATM carrier status was significantly increased in patients with a Gleason score of 9–10 corresponding to grade group 5 and high-grade cancer, compared to Gleason scores 2–6 (grade group 1) (3.47% and 0.20%, respectively)

(Wu et al., 2020). This further substantiates the value of germline ATM mutation analysis in enhanced screening for PCa to better inform diagnoses, as well as to predict response to other therapeutics such as PARPis. However, an important logistical problem arises when one considers how screening assays could be conducted for enrolment into biomarker-driven targeted therapies. Whilst germline sequencing of ATM mutants correlates with PCa development and progression, a recent study found that approximately 1 in 4 PCa patients with germline mutations still possess protein expression and lack biallelic inactivation (Kaur et al., 2020). ATM loss as determined by immunohistochemistry (IHC) was found in > 10% of advanced PCa samples in a study, and this feature correlated with genomic instability but not complete loss of HR-mediated DNA repair (Neeb et al., 2021). Based on this, Kaur et al. (2020) developed an IHC assay to measure ATM protein loss, which in combination with next-generation sequencing could be used to identify ATM-deficient tumours and stratify cohorts likely to benefit from specifically targeted therapies.

3.2.3. ATM deficiency to sensitise PCa cells to PARP inhibition

As previously covered above, ATM mutations are a frequent feature of many cancers and occur in approximately 5–10% PCa tumours (Jette et al., 2020a; Rafiei et al., 2020), prompting research into how its deficiency could sensitise cancer cells to PARP inhibition. In the clinical trial TOPARP-A, Mateo et al. (2015) tested pharmacological PARP inhibition in 49 mCRPC patients with Olaparib. Fresh patient biopsies were analysed via NGS and a subset of patients with genomic alterations in BRCA1/2, ATM, PALB2, CHEK2, FANCA and HDAC2 exhibited a higher sensitivity and response rate of 88% to Olaparib, presenting the potential of these DDR genes as predictive biomarkers for PARP inhibitor sensitivity in mCRPC (Mateo et al., 2015). In the follow up study, TOPARP-B, 21 mCRPC patients with ATM loss were treated with Olaparib, however anti-tumour activity was minor in comparison to patients with BRCA-mutations. Whilst a subset of patients with ATM aberrations benefited from the trial, it was concluded that solely measuring ATM genomic alterations might not be extensive enough to accurately predict PARPi-sensitivity (Mateo et al., 2020). Rafiei et al. (2020) further confirmed that CRISPR/Cas-9 mediated ATM knockout or siRNA mediated ATM knockdown only minimally sensitised PCa cells to PARP inhibition, suggesting context dependent sensitivity which partially explains the variable responses seen in clinic in ATM-deficient cancers.

It is important to note that inactivation of ATM as opposed to ATM deletion in cells embodies a distinct phenotype, suggesting that perhaps combined PARPi and ATMi could represent a viable therapeutic strategy in PCa (Rafiei et al., 2020). Similarly, whilst ATM deficiency in cancer is most studied, its abnormal activation has also been shown to sensitise cells to PARPis, with ATM phosphorylation enhanced by PPP2R2A inhibition impairing HR-mediated DNA repair (Kalev et al., 2012). In PCa tumours, a study found that 61.7% samples contained PPP2R2A deletions (Cheng et al., 2011). Ultimately, this suggests that exploiting precisely coordinated activation and inhibition of ATM could be used to inhibit DNA repair and subsequently sensitise cells to treatments.

3.2.4. ATR inhibition in PCa

Whilst PARP inhibition appears to have been the predominant focus in DDR-targeted treatments, other DNA damage associated proteins also represent attractive options.

Inhibition of ATR has become an area of much interest lately due to its promising potential in preclinical studies. ATM and PARP can function in independent DDR pathways, therefore parallel inhibition of these two signalling proteins can overcome different mechanisms of DNA damage repair to synergistically improve antitumor efficacy and counteract PARPi resistance. This concept has been investigated by Wengner et al. (2020) through the concomitant use of BAY 1895344 (ATR inhibitor) and Olaparib, a combination which enhanced tumour reduction in both PARPi-sensitive breast and prostate cancer xenografts. Additionally, BAY 1895344 in combination with the AR-antagonist Darolutamide led to reduced DDR gene expression in cultured PCa cells, as well as enhanced antitumour activity in an in vivo PCa model, suggesting that a combination therapy of ATR inhibition (ATRi) with AR inhibition represents a feasible therapeutic strategy in AS PCa tumours. Combining this approach with radiation therapy further enhanced the anti-tumour efficacy, proposing further research into combined AR-targeted therapies with ATRi (Rafiei et al., 2020). Recently, the first phase I clinical trial involving patients taking oral BAY 1895344 revealed both its tolerability and efficacy in patients with advanced solid tumours, including PCa (Yap et al., 2021). Other clinical trials are underway for this ATR inhibitor in patients with advanced solid tumours (NCT03188965), as well as a phase II trial in combination with PARPi in mCRPC (NCT03787680). In prostate cancer, ATR inhibition abrogates ATR-Chk1 signalling leading to destabilisation and degradation of PD-L1. Synergistic effects were observed between combined ATRi and anti-PD-L1 ICI treatments which could augment T-cell mediate cell death and subsequently enhance the safety and efficacy of ICI (Tang et al., 2021). This nicely highlights the potential for dual targeting of DDR machinery and ICI in cancers such as PCa and this approach is already being tested in clinical trials combining Ceralasertib with durvalumab in gastric cancer and melanoma (NCT03780608).

3.2.4.1. Synergistic ATR inhibition in ATM-deficient PCa. The effects of combined ATRi with other current molecular inhibitors or therapeutic strategies shows clear potential, yet the synergistic efficacy of ATRi in ATM-deficient cancers has not yet been discussed and represents an extremely attractive therapeutic option.

A synthetically lethal relationship exists between ATM and ATR, and ATRi promotes selective induction of cell death in ATM-deficient cell lines (Min et al., 2017). Whilst PARPi in ATM-deficient cancers has generated varying degrees of therapeutic efficacy, in ATM-deficient prostate cancer models ATRi sensitivity was robustly enhanced in comparison to PARPi sensitivity (Rafiei et al., 2020). Since ATM inactivation frequently occurs in metastatic PCa, this represents a promising arena for a stratified treatment regime.

The emergence of this synergistic relationship has led to numerous investigations on both monotherapy and in combination with other treatments. For example, Lloyd et al. (2020) demonstrated that Olaparib in combination with the ATRi Ceralasertib (AZD6738) further enhanced antitumour activity in ATM-deficient cancer cell lines, as well as in vivo patient derived xenograft (PDX) mouse models with ATM-loss. This combined approach led to the rapid killing of tumour cells which could allow low-dose combination therapy to circumvent the associated toxicity observed with high-dose monotherapy, as well as reduced need for continuous prolonged treatment, whilst achieving effective antitumour efficacy. Jette et al. (2020b) generated an ATM-deficient PCa cell line and found that Olaparib treatment alone decreased proliferation however only combined Olaparib + ATRi induced apoptosis (Kumar et al., 2020a). Similarly, in ATM-proficient cells, combined PARPi and ATRi treatment had little effect. This further substantiates the superior dual efficacy of PARP and ATM inhibition in ATM-depleted PCa, however it also highlights the importance of how sensitivity is assessed (ie. cell viability or apoptosis measurements). Another study further corroborated this in ATM-knockdown PCa cell lines and an ATM-knockout PDX mouse model whereby single-agent ATR inhibition exhibited superior antitumour activity in comparison to PARP inhibition, with combined treatment further enhancing efficacy than either treatment alone (Neeb et al., 2021). These findings support further clinical research into stratifying PCa patients based on ATM deficiency for combination therapy with ATR and PARP inhibition, however further research is required to define exactly how distinct ATM mutations affect sensitivity (such as deletions, truncation, and missense mutations) (Rafiei et al., 2020).

At the moment, many clinical trials are underway looking at different

Table 1
ATR inhibitors in clinical trials specifically for prostate cancer treatment.

Drug	Clinical Trials	Combined treatment	Disease specifics	Phase
Ceralasertib (AZD6738)	NCT04564027	N/A	ATM-altered mCRPC	II
Ceralasertib (AZD6738)	NCT03787680	Olaparib	DDR-deficient mCRPC	II
Berzosertib (VX-970/M6620)	NCT03517969	Carboplatin with or without Docetaxel	mCRPC and stage IV PCa	II
Berzosertib (VX-970/M6620)	NCT03718091	N/A	Advanced solid tumours with HR mutations, and truncating ATM mutations	II
Berzosertib (VX-970/M6620)	NCT03641547	Cisplatin & Campecitabine	Advanced solid tumours	I
Elimusertib (BAY1895344)	NCT04095273	Pembrolizumab	mCRPC with ATM mutation or ATM-loss	I
Elimusertib (BAY1895344)	NCT03188965	N/A	Advanced solid tumours including mCRPC	I
Elimusertib (BAY1895344)	NCT05010096	Copanlisib	Advanced solid tumours including mCRPC	I

Table 2
ATM inhibitors currently undergoing clinical trials in cancer patients.

Drug	Clinical Trials	Combined treatment	Conditions	Phase
M3541	NCT03225105	Radiotherapy	Solid tumours	I
KU-60019	NCT03571438	CX4945 (CDK2 inhibitor)	Renal tumours	N/A
AZD0156	NCT02588105	Olaparib, Irinotecan, Fluorouracil, Folinic acid	Advanced malignancies	I
AZD1390	NCT03423628	Radiotherapy	Glioblastoma, or brain metastases	I
AZD1390	NCT04550104	Radiotherapy, Olaparib,other compounds TBD	Non-small cell lung cancer (NSCLC)	I
AZD1390	NCT05182905	N/A	Glioblastoma	Early phase I
AZD1390	NCT05116254	Radiotherapy	Soft tissue sarcomas	I

ATR inhibitors as monotherapies or in combination with other treatments, including radiation, chemotherapy, immunotherapy and PARP inhibitors. ATR inhibitors currently in clinical development include Ceralasertib, Berzosertib (VX-970) and BAY1895344. In prostate cancer, ATR inhibitors are being investigated in many clinical trials (see Table 1). For example, a phase II trial is investigating Ceralasertib efficacy in a panel of ATM-altered mCRPC patients, where the selected cohort has at least 60% cases with ATM IHC $\leq$ 5% (NCT04564027). Phase II trials are also assessing combined ATRi and PARPi with Olaparib and Ceralasertib in patients with DDR-proficient and DDR-deficient mCRPC (NCT03787680), as well as in general HR-deficient cancers (NCT02576444).

Further clinical trials are also in progress evaluating ATRi in cancers in general, such as.

Ceralasertib in combination with Gemcitabine in advanced solid cancers (NCT03669601) and in combination with paclitaxel in refractory cancers (NCT02630199). Additionally, berzosertib is under investigation in combination with the immunotherapeutic Avelumab DDR-deficient cancers (NCT04266912).

Whilst ATR inhibitors are being extensively appraised, trials involving ATM inhibitors are less common. As noted, ATM deficiency is a general trend observed in cancers, which could enhance other DNA damage targeting treatment options, however cancers with normal ATM expression have also to be considered. ATRi and PARPi in ATM expressing malignant cells had minimal effect in comparison to ATM-deficient cancers (Kumar et al., 2020a). This highlights the importance of ATM function in DNA damage repair and treatment resistance. In this light, there is a renewed interest in measuring ATM activity and expression in diseases such as PCa to optimise treatment based on stratified groups. Using ATM inhibitors to convert an ATM-proficient tumour into an ATM-deficient tumour could sensitise these cancers to other therapies. In terms of PCa, ATM inhibition in PCa cells exhibiting inactivated AR promotes cell death, suggesting its potential use in combination with AR-targeted therapies would be warranted (Reddy et al., 2015). Whilst there are currently no clinical trials assessing ATM inhibition in PCa, others investigating novel ATM inhibitors in other cancers are currently underway (see Table 2).

4. Conclusion

This review consolidates a substantial body of evidence that purports the vital roles of ATM and ATR in the orchestration of the DDR pathway in supporting maintenance of genomic stability that allows normal cell survival. The review also highlights the obvious potential of targeting these kinases to sensitise cancer cells to cytotoxic treatments. A key take-home message from the current research is the synergistic lethality observed between ATM loss and ATR inhibition, which represents an extremely attractive therapeutic strategy for ATM-deficient PCa (Neeb et al., 2021). The literature described here also substantiates the potential of ATM as a molecular biomarker to stratify PCa patients and enhance ATRi sensitivity, which may aid in prognosis and decisions on active surveillance, as well as screening strategies (Giri et al., 2020). Additionally, the feasibility of therapeutically targeting ATR in ATM-deficient tumours, as well it's synergistic activity in combination with other therapies, may provide new treatment options for PCa patients, and enhance efficacy of current therapies whilst overcoming mechanisms of therapeutic resistance.

The next stages in the ongoing development of ATR/ATM-based therapies, and in particular ATR inhibition in ATM-deficient PCa, will involve intense focus on rational drug combinations and identification of further genomic alterations that will confer ATRi sensitivity (Mateo et al., 2020; Rafiei et al., 2020). Conceptually, the use of ATM inhibitors in ATM-proficient PCa tumours could represent a further therapeutic advance to enhance sensitivity to ATR and PARP inhibitor treatments, an area which needs further exploration. Overall, the importance of ATM and ATR is becoming increasingly evident for optimal screening and risk stratification, as well as their positions as attractive therapeutic targets for PCa in this evolving era of precision medicine.

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